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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/591,097	RODRIGUEZ ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *4-7 and 12-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 8-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/6/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-12, and the combination of genes of ADAM9, BUB1B, gene 85, gene 84(MCP; referred to in the response as CD46), GJAI, HIFIA, ITGBI, LAMBI, MAD2L1, gene 13 (hypothetical protein FLJ20373), PRPF40A, PSMC6, RANBP2, gene 58 (CSPG6), SP3, THBS1, TTK, gene 98 (FNBP3), TOB1, and gene 73 (acidic (leucine-rich) nuclear phosphoprotein 32 family, member E) in the reply filed on July 13, 2009 is acknowledged. The traversal is on the ground(s) that the inventions of Group I and II share a corresponding special technical feature in that the methods of groups I and II both require assaying for the expression of a gene by exposing a cell (Group I) or a subject (Group II) to a compound. This is not found persuasive because the technical feature of assaying for the expression of a gene in a cell or subject following exposure of the cell or subject to a compound was known in the art at the time the invention was made and was specifically disclosed by Mack et al (PGPUB 2004/0005563; cited in the restriction requirement of 4/17/09). Further, the prior art of Li et al (J. Nutrition. 2003. 133: 1011-1019; discussed in detail below) discloses methods comprising providing PC3 human prostate cancer cells, measuring expression by the cell of each of the 22,215 genes which hybridize to the probes present in the Affymetrix U133 Array, exposing the cells to the compounds indole-3-carbinol (IC3) and 3,3'-dinodolylmethane (DIM), and determining the expression of each of the 22,215 genes which hybridize to the probes present in the Affymetrix U133 array. Thus, Li teaches the technical feature linking the inventions of Group I and II of

determining the expression level of the 20 genes from Table 1 prior to and following exposure to a test compound. Thereby, the claims of Groups I and II do not share a special technical feature, as is necessary to fulfill the requirement for unity of invention.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-34 are pending. Newly added claim 34 recites "up-regulated by lunasin by at least two-fold." It is unclear as to what subject matter this claim is drawn to. To the extent that this claim may be directed to a nucleic acid that is up-regulated by lunasin at least two-fold, this subject matter does not share a special technical linking feature with the elected Group I of methods of screening test compounds for anti-neoplastic activity.

Claims 1-3 and 8-11 are directed to the elected invention and have been examined herein to the extent that the claims read on the elected combination of genes. The non-elected combinations of genes recited in claims 1-3 and 8-11 are withdrawn from consideration.

Claims 4-7 and 12-34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on July 13, 2009.

Claim Objections

3. Claims 1-3 and 8-11 are objected to because the claims reference tables of the specification. Claims which recite figures or tables are only permitted in exceptional circumstances where there is no practical way to define the invention in words and

where it is more concise to incorporate by reference than duplicating a drawing or table into a claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112 first paragraph

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 and 8-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to methods which require detecting the expression of the 20 elected genes from Table 1. In the reply of July 13, 2009, Applicants indicate that the 20 elected genes include Gene 85 "also called 'CD44,' Gene 13 from Table 1 (also called "FLJ20373" or "MAP4K4") , Gene 98 from Table 1 (also called "forming binding protein 3" or "PRPF40A"), Gene 58 from Table 1 (also called "CSPG6" or "SMC3") and Gene 73 from Table 1 (called "Acidic (leucine-rich) nuclear phosphoprotein 32 family, member E").

Table 1 of the specification includes columns for a gene number, an Affymetrix probe set number, a Gene identifier, a Gene Name, and an "Official Gene Symbol."

Regarding the elected "Gene 85" gene, the specification and particularly Table 1 do not refer to a "CD44" gene. Rather, Table 1 lists a "Gene 85" and an Affymetrix

probe set number of “217523_at”. A Gene identifier is not provided, nor is an official gene symbol. For the Gene Name, Table 1 recites "Data not available." The information that Gene 85 may intend to encompass the CD44 gene can only be ascertained by referring to the Affymetrix product information for the probe sets present in the U133A GeneChip. By referring to Affymetrix probe set number for Gene 85, or any of the other elected genes set forth in Table 1, the claims seek to incorporate by reference the subject matter of the sequences set forth in the Affymetrix product information for the U133A GeneChip. Similarly, by referring to Gene Identifiers, the claims seek to incorporate the subject matter of the sequences recited in databases, such as NCBI records and Ensembl records. This constitutes an improper incorporation by reference to essential subject matter since this subject matter is necessary to describe the claimed invention. Essential material may not be incorporated by reference to non-patent publications (see MPEP 608.01(p)). Therefore, to the extent that the claims encompass detecting “Gene 85” defined by the Affymetrix probe set 217523_at, or encompass any of the other genes defined by the Affymetrix probe set or Gene Identifier numbers recited in Table 1, the claims are rejected for failure to comply with the enablement requirement because the specification fails to provide essential subject matter for the practice of the claimed invention.

To any extent that the claims intend to recite only the gene numbers listed in Table 1, this subject matter is not considered to be enabled because the specification has not adequately defined the gene numbers per se. For instance, the specification does not clearly set forth that “Gene 6” is intended to be limited to the GJA1 gene.

Because it is unclear as to what constitutes "Gene 6" or "Gene 7" or "Gene 13" etc, one of skill in the art can not predictably practice the claimed invention which requires detecting an increase in the expression of such genes.

Moreover, it is noted that the reply of July 13, 2009 indicates that Gene 13 from Table 1 is also called FLJ20373 or MAP4K4. However, Table 1 indicates that Gene 13 is referred to only as "hypothetical protein FLJ20373). The reply indicates that Gene 98 from Table 1 is also called "forming binding protein 3" or "PRPF40A." However, the specification does not define Gene 98 as "PRPF40A." The reply also indicates that Gene 58 from Table 1 is also called "CSPG6" or "SMC3. " However, the specification does not define Gene 98 as "SMC3."

Further, the following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims:

The claims are drawn to methods for screening a test compound for anti-neoplastic activity comprising providing a cell, measuring expression by the cell of a plurality of genes, exposing the cell to a test compound, and re-measuring the expression of the plurality of genes, wherein the degree of increase in expression by the

cell of the genes "corresponds" (i.e., is similar to or in agreement with) the degree of anti-neoplastic activity of the test compound.

In particular, the plurality of genes include:

ADAM9, BUB1B, gene 85 of Table 1, gene 84 of Table 1 (MCP; referred to in the response as CD46), GJAI, HIFIA, ITGBI, LAMBI, MAD2L1, gene 13 (hypothetical protein FLJ20373), PRPF40A, PSMC6, RANBP2, gene 58 of Table 1 (CSPG6), SP3, THBS1, TTK, gene 98 of Table 1 (FNBP3), TOB1, and gene 73 of Table 1 (acidic (leucine-rich) nuclear phosphoprotein 32 family, member E).

The claims broadly recite providing a cell, and thereby the cell may be obtained from any human or non-human subject, such as a horse, dog, goat, elephant, panda etc, and may be any type of cell, including a skin cell, a cell present in urine or feces, a colon cell, a brain cell, a lung cell, a blood cell, or any type of cancer cell.

Nature of the Invention

The claims encompass screening a test compound for anti-neoplastic activity by assaying for gene expression of a plurality of genes. The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Teachings in the Specification and State of the Art:

The specification teaches that the compound lunasin suppresses chemically-induced carcinogenesis in mammalian cells and suppresses skin tumor formation in

mice (page 5, para [15]). It is stated that transfection of a cell with lunasin leads to cell death and that lunasin peptide has been shown to have anti-neoplastic properties.

The specification (page 13) provides the results of an expression profile study in which the U133A GeneChip was utilized to determine RNA levels of 22,215 transcripts in Rostate epithelial cells, RWPE-1 (normal) and RWPE-2 (malignant). The study measured RNA levels both in cells exposed to lunasin for 24-hours and in untreated cells. The specification teaches that 123 genes had a greater than two-fold change in expression in treated versus untreated cells (page 14). In particular, 121 genes were up-regulated in lunasin treated RPWE-1 (normal) cells and 2 genes were up-regulated in lunasin treated RPWE-2 (malignant) cells (page 14).

With respect to the elected invention, ADAM9, BUB1B, gene 85 of Table 1, gene 84 of Table 1 (MCP; referred to in the response as CD46), GJAI, HIFIA, ITGB1, LAMB1, MAD2L1, gene 13 (hypothetical protein FLJ20373), PRPF40A, PSMC6, RANBP2, gene 58 of Table 1 (CSPG6), SP3, THBS1, TTK, gene 98 of Table 1 (FNBP3), TOB1, and gene 73 of Table 1 (acidic (leucine-rich) nuclear phosphoprotein 32 family, member E) were each up-regulated in normal RWPE-1 epithelial cells after 24-hours of exposure to lunasin (see Table 1).

The Predictability or Unpredictability of the Art and Quantity of Experimentation:

The art of determining an association between gene expression levels and the occurrence of a phenotype, such as response to therapy for an autoimmune disease, is highly unpredictable. Gene expression may be influenced by a number of factors, in addition to disease itself, and these factors must be considered prior to drawing any

conclusions regarding an association between gene expression patterns and the occurrence of disease or response to treatment for a disease.

The specification (para [15]) states that "(v)arious genes found by this study to be up-regulated by lunasin are known to play a role in cell growth, differentiation and tumor suppression and other important physiological activity directly or indirectly related to neoplastic transformation. It is therefore reasoned that lunasin suppresses neoplastic transformation by up-regulating various genes." It is also stated that "(v)arious genes found by this study to be up-regulated by lunasin are known to play a role in cell growth, differentiation and tumor suppression and other important physiological activity directly or indirectly related to neoplastic transformation. It is therefore reasoned that lunasin suppresses neoplastic transformation by up-regulating various genes" (para [16]).

However, the specification does not in fact establish that the 20 elected genes, alone or in combination, alter the neoplastic properties of a cell in vitro or in vivo when expressed at increased levels. While particular individual genes may have activities associated with apoptosis or cell growth, this fact does not allow one to reasonably whether increasing the expression of these genes will result in a decrease in the neoplastic properties of a cell expressing these genes.

Further, the results in the specification for the 20 elected genes are limited to gene expression levels in RWPE-1 cells, an immortalized human prostate cell line. However, it is unpredictable as to whether the results obtained with a single immortalized human prostate cell line in vitro would be predictive of the results obtained in other cancer and non-cancer cell lines or primary cells. Modification of gene

expression may occur in all cells or may only occur in a subset of cells that are directly involved in a disorder, such as cancer. For example, it is unpredictable as to whether any primary cell, such as a primary skin cell or muscle cell in response to treatment with a test compound as indicative of anti-neoplastic activity of the test compound. One cannot determine apriori which cells will show an altered gene expression that can be used to identify a test compound as anti-neoplastic. Such information can only be obtained through experimentation.

The unpredictability in the art is supported by the teachings of Singh et al (Proceedings of the New Zealand Society of Animal Production. 2004. 64: 8-10). Singh teaches the unpredictability in the art of using microarray analysis to determine an association between gene expression levels and phenotypes. Singh (page 10) states that "(c)onsidering the level of changes in gene expression and array hybridization intensity, validation of differentially expressed genes identified by microarray analysis is required (Rajeevan et al. 2001). Our results show the level of gene expression can be different between the cDNA microarray and the sensitive real-time RT-PCR analysis. This is in agreement with previous DNA microarray experiments which suggest the true expression differences for specific members of gene families may be masked by cross-hybridisation in microarrays."

The teachings of Schmidt (Blood. 1998. 91(1): 22-29) highlight the unpredictability of extrapolating expression profile results obtained with one type of cancer to other types of cancer. In particular, Schmidt teaches while that reduced

expression of ICSBP is associated with AML and CML, altered ICSBP expression was not associated with lymphatic neoplasias (see page 24 of Schmidt).

The prior art of , Ruzkijic et al. (US Pat. 5,990,299, November 1999) supports the unpredictability of extrapolating gene expression results from one type of cancer to other types of cancer and the unpredictability of assaying for the expression of genes that undergo differential splicing. Ruzkijic teaches that "In some studies over-expression of only particular variants has been associated with cancers. For example, expression of variants containing exon v6 sequences occurs in the advanced stages of the development of some tumors, but some CD44 variants without exon v6 sequences appear at the earliest stage of tumorigenesis and in early adenomas. Screening of gastric adenocarcinoma has revealed CD44v expression in all tested specimens, with intestinal type adenocarcinomas expressing variant exons v5 and v6, and diffuse-type adenocarcinomas predominantly expressing only exon v5. Normal stomach mucosa has shown exon v5 expression within the foveolar proliferation zone and on mucoid surface epithelium. The same pattern of expression has been confirmed for exon vl 1 abundantly present in well differentiated intestinal tumors in comparison with diffuse type cancer tissues. Normal gastric mucosas have demonstrated significantly lower expression of exon vl 1 splice forms. CD44 presence has been associated with tumor recurrence and increased mortality during follow-up averaging 14 months." Therefore, the art supports the concept that not all variants and members of a particular gene are similarly associated with different types of cancer.

The teachings in the prior art of Oguri (International Journal of Cancer. 2000.86: 95-100) highlight the unpredictability of interpreting gene expression obtained results *in vitro* as indicative a drugs anti-neoplastic activity. Oguri studied MRP5 mRNA levels in both normal lung and lung cancer cells *in vitro* and *in vivo* following exposure to carboplatin (page 99). MRP5 mRNA levels were significantly higher in cells from patients who had been previously exposed to platinum drugs *in vivo* than from patients who had not been previously exposed to platinum drugs (page 98, col. 2). The authors also report that MRP5 mRNA levels were not rapidly induced by platinum drugs either in lung cancer cell lines or in PMN cells within 24 hours (see abstract). The teachings of Oguri highlight the unpredictability in the art and the variety of factors which must be considered when interpreting results of screening assays, including time of exposure to an agent, use of cells previously exposed to an agent as compared to cells not previously exposed to an agent, and the relevance of comparing gene expression levels in normal cells and cancer cells.

Similarly, Li et al (Journal Nutrition. 2003. 133: 1011-1019) analyzed gene expression in PC3 human prostate cancer cells treated with I3C and DIM. I3C is known to inhibit the growth of PC3 prostate cells in vivo and DIM is an in vivo dimeric product of I3C (see abstract). Li noted differences in the gene expression patterns following exposure of the cells to I3C or DIM for 6 hours, 24 hours and 48 hours (see Table 3). Li also observed differences in the expression patterns for genes known to be associated with apoptosis and cell growth in I3C treated cells as compared to DIM treated cells (Table 3).

It is also noted that the specification does not provide a clear definition for what is intended to be encompassed by "anti-neoplastic." To the extent that this is intended to indicate that a test compound will control the growth of or kill a neoplastic cell in vivo, it is unpredictable as to whether the expression data results obtained in vitro with lunasin can be extrapolated to cancer cells in vivo. It is well accepted that the genetic alterations which occur in cell lines are not necessarily reflective of the genetic changes which occur *in vivo*. For instance, Dermer, G.B. (Bio/Technology (1994) 12: 320) states that "The cell lines in which cancer is usually studied are unsuitable for the job. They do not mimic conditions in the human body." Dermer concludes that "Petri dish cancer is really a poor representation of malignancy, with characteristics profoundly different from the human disease." Since the results obtained in vitro in cell lines cannot be extrapolated to in vivo, knowledge that a combination of genes are overexpressed in vitro in response to treatment with one known "anti-neoplastic" drug (i.e., lunasin), does not allow one to conclude that overexpression of these genes is correlated with anti-neoplastic activity of other drugs *in vivo*.

Amount of Direction or Guidance Provided by the Specification:

The specification does not provide any specific guidance as to how to extrapolate the findings obtained with RWPE-1 cells and treatment with lunasin to a representative number of other cancer or non-cancer cell lines or primary cells or to test compounds of unknown activity. There is no specific guidance provided in the specification as to the types of cells in which one would expect to detect the same change in level of the 20 elected genes in response to a compound having anti-

neoplastic activity. Thus, one of skill in the art would be left to randomly screen for possible additional cancer and non-cancer cell lines and primary cells that show a similar expression pattern of an increase in the level of the 20 recited genes in response to exposure to a compound that has anti-neoplastic activity.

While methods for expression profiling are known in the art, such methods provide only the general guidelines that allow researchers to randomly search for genes whose expression may linked to a phenotype, such as cancer or response to a drug used to treat cancer. The results of performing such methodology are highly unpredictable. The specification has provided only an invitation to experiment. The specification does not provide a predictable means for identifying additional cells whose increase in expression of the 20 elected genes in response to treatment with a compound is indicative of a compound that is anti-neoplastic.

Working Examples

The specification does not provide a single example of a method in which a test compound is effectively identified as being neoplastic by assaying for an increase in the level of expression of the 20 recited genes in cells treated with the test compound, as compared to untreated cells. Rather, the specification exemplifies only methods in which immortalized human prostate RWPE-1 cells were exposed to a known anti-neoplastic agent, lunasin, and an increase in the level of the 20 elected genes was detected as compared to cells that were not treated with lunasin.

Conclusions:

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In the instant case, the specification has not enabled the claimed invention because the specification teaches only the results of expression profiling in a human prostate cancer cell line (RWPE-1) treated with lunasin, but does not teach an association between an increase in expression of the recited genes and anti-neoplastic activity. Additionally, for the reasons discussed in detail above, the specification does not teach how to make and use the claimed invention because the specification does not adequately teach the identity of each of the claimed genes so that one could predictably detect an increase in expression of each of the claimed genes as indicative of anti-neoplastic activity of a test compound. Further, the claims do not bear a reasonable correlation to the scope of enablement because the specification and prior art do not teach a representative number of additional cancer cell types that express the

combination of the 20 elected genes at increased levels in response to lunasin, or any other test compound having anti-neoplastic activity. Accordingly, in view of the unpredictability in the art, and the lack of disclosure in the specification and in the prior art, it would require undue experimentation for one of skill in the art to make and use the invention as broadly claimed.

5. The incorporation of essential material in the specification by reference to an unpublished U.S. application, foreign application or patent, or to a publication is improper – i.e., the incorporation of the gene sequences by reference to the Affymetrix probe sets or the gene identifiers provided in databases, such as the NCBI GenBank Database or the Ensemble Database. Applicant is required to amend the disclosure to include the material incorporated by reference, if the material is relied upon to overcome any objection, rejection, or other requirement imposed by the Office. The amendment must be accompanied by a statement executed by the applicant, or a practitioner representing the applicant, stating that the material being inserted is the material previously incorporated by reference and that the amendment contains no new matter. 37 CFR 1.57(f).

Claim Rejections - 35 USC § 112 second paragraph

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3 and 8-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 1-3 and 8-11 are indefinite. The claims are drawn to a method for screening a test compound for anti-neoplastic activity. The claims recite a final step of measuring expression by the cell of a plurality of genes. The claims further recite a wherein clause that indicates that the degree of increase in expression of the plurality of genes "corresponds" (i.e., is similar to or in agreement with) to the degree of anti-neoplastic activity of the test compound. The claims do not, however, recite an active process of determining whether a test compound has anti-neoplastic activity. The recitation regarding the fact that the degree of expression corresponds to the degree of anti-neoplastic activity indicates only an inherent property of the degree of increase in expression. This recitation is not equivalent to reciting a step that determines whether a test compound does or does not have anti-neoplastic activity. It is hereby unclear as to whether the claims are intended to be limited to a method which only determines the expression of the plurality of genes prior to and following exposure to a test compound or if the claims are intended to be limited to methods which determine if a test compound has anti-neoplastic activity. In the later case, the claims omit the essential process step of determining that the test compound does or does not have anti-neoplastic activity. See MPEP § 2172.01. Note that MPEP 2773.02 states that if the language of the claim is such that a person of ordinary skill in the art could not interpret the metes and bounds of the claim so as to understand how to avoid infringement, a rejection of the claim under 35 USC 112, second paragraph, is appropriate.

B. Claims 1-3 and 8-11 are indefinite. The claims encompass the detection of the 20 elected genes set forth in Table 1. However, the specification does not provide a

clear definition for what is intended to be encompassed by each of the 20 elected genes set forth in Table 1. In the reply of July 13, 2009, Applicants indicate that the 20 elected genes include Gene 85 "also called 'CD44,' Gene 13 from Table 1 (also called "FLJ20373" or "MAP4K4") , Gene 98 from Table 1 (also called "forming binding protein 3" or "PRPF40A"), Gene 58 from Table 1 (also called "CSPG6" or "SMC3") and Gene 73 from Table 1 (called "Acidic (leucine-rich) nuclear phosphoprotein 32 family, member E"). Table 1 of the specification includes columns for a gene number, an Affymetrix probe set number, a Gene identifier, a Gene Name, and an "Official Gene Symbol." Regarding the elected "Gene 85" gene, the specification and particularly Table 1 do not refer to a "CD44" gene. Rather, Table 1 lists a "Gene 85" and an Affymetrix probe set number of "217523_at". A Gene identifier is not provided, nor is an official gene symbol. For the Gene Name, Table 1 recites "Data not available." Accordingly, the specification and claims do not clearly define what is intended to be encompassed by "Gene 85." Further, to the extent that the claims seek to refer to the information provided at the Affymetrix web site or in Affymetrix product information for the U133A GeneChip or to Gene Identifier numbers set forth in database entries, such as the NCBI GenBank or Ensembl, these sources and database entries include a variety of information. It is unclear as to which characteristics disclosed for each entry are intended to be encompassed by the recited terms. Moreover, the information in databases and product information varies over time and is not fixed. Therefore the recitation of Affymeterix probe set numbers and NCBI and Ensembl Gene Identifiers, in the absence of a clear definition for these terms in the specification, renders the claims unclear and indefinite.

additionally, to any extent that the claims intend to recite only the gene numbers listed in Table 1, the specification has not adequately defined the gene numbers per se. For instance, the specification does not clearly set forth that "Gene 6" is intended to be limited to the GJA1 gene. Accordingly, one of skill in the art would not be able to determine the meets and bounds of the claimed subject matter to the extent that the claims encompass genes defined only by a gene number.

Priority

7. The present claims are not entitled to Provisional Application 60/549487, filed March 1, 2004 because the '288 application does not disclose methods for screening a test compound for anti-neoplastic activity by assaying for the expression level of each of the 20 elected genes.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3 and 8-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Li et al (Journal Nutrition. 2003. 133: 1011-1019), as evidenced by the present specification (page 13, para [40]).

As noted in the MPEP 211.02, "a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for

completeness but, instead, the process steps or structural limitations are able to stand alone." Further, in *Pitney Bowes Inc. v. Hewlett-Packard Co.*, 182F.3d 1298, 1305, 51 USPQ2d 1161, 1166 (Fed Cir. 1999) the court held that if the body of the claim sets forth the complete invention, and the preamble is not necessary to give "life, meaning and vitality" to the claim, "then the preamble is of no significance to claim construction because it cannot be said to constitute or explain a claim limitation". In the present situation, the claim language of "for screening a test compound for anti-neoplastic activity" is a statement of purpose and intended result and does result in a manipulative difference in the method steps of the claims. While the claims recite a wherein clause that states that the degree of increase in expression of the plurality of genes corresponds to the degree of anti-neoplastic activity of the test compound, this clause indicates only what is an inherent to the increase in expression. This clause is not equivalent to reciting an active process step of determining that the test compound has anti-neoplastic activity. Accordingly, the process steps are able to stand alone and therefore the preamble limitation is not accorded patentable weight. Thereby, the present claims are considered to encompass methods which require only determining the level of expression of the plurality of genes prior to and following exposure to a test compound.

Li et al (page 1012) disclose methods comprising providing PC3 human prostate cancer cells, measuring expression by the cell of each of the 22,215 genes which hybridize to the probes present in the Affymetrix U133 Array, exposing the cells to the compounds indole-3-carbinol (IC3) and 3,3'-dinodolylmethane (DIM), and determining

the expression of each of the 22,215 genes which hybridize to the probes present in the Affymetrix U133 array. The Affymetrix U133 array comprises each of the presently claimed 20 genes, as evidenced by the specification (page 13, para [40]). Thereby, Li teaches the presently claimed method in which expression levels of the 20 elected genes from Table 20 are determined prior to and following exposure with a test compound (i.e., the anti-neoplastic compounds IC3 and DIM). It is considered to be a property of the degree of increase in the expression of the genes that the degree of increase in expression corresponds to the degree of anti-neoplastic activity of the test compound.

Further, it is noted that Li teaches that I3C inhibits the growth of PC3 prostate cancer cells and induces apoptosis by inhibiting nuclear factor (NF)-κB and Akt signaling pathways, suggesting that I3C may serve as a preventive and/or therapeutic agent against prostate cancer (page 1012, col. 1). Li identified a total of 685 genes down-regulated in response to I3C and 42 genes up-regulated in response to I3C, and 677 genes down-regulated in response to DIM and 61 genes up-regulated in response to DIM.

Regarding claim 2, Li teaches normalizing the gene expression levels to obtain a mean intensity equivalent and using software programs to obtain average differences of gene expressions between two or several samples (page 1012, col. 2). Thereby, Li is considered to teach methods wherein the degree of increase of a plurality of genes is measured using a weighted average.

Regarding claim 3, the method of Li includes identifying genes whose expression is at least two-fold (page 1012 and Table 3).

Regarding claim 8, it is a property of the 22,215 genes assayed for expression in the method of Li, including the presently claimed 20 genes, that these genes comprise genes that regulate apoptosis, suppress cell proliferation, are mitotic check point genes, are involved in protein degradation and up-regulate gap junction proteins (see Tables 1 and 2).

Regarding claims 9-11, in the method of Li, gene expression is measured using an array comprising a plurality of probes affixed to a substrate (i.e., the Affymetrix U133A Arrray) and the probes are complementary to at least the 20 elected genes of present Table 1 (see page 1012).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is 571-272-0747. The examiner can normally be reached on Monday-Thursday (6:30-5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Carla Myers/

Primary Examiner, Art Unit 1634